

AMENDMENT TO THE SPECIFICATION

This listing of claims will replace all prior versions of claims in the application.

Listing of Claims:

1. (Currently Amended) A substantially pure nucleic acid molecule having at least 90% sequence identity to SEQ ID NO: 1 and encoding a mammalian methionine synthase reductase polypeptide, wherein said polypeptide is capable of catalyzing the reductive methylation of methionine synthase-cob(II)alamin to generate methionine synthase-cob(III)alamin-CH₃.
2. (Currently Amended) The nucleic acid molecule of claim 1, wherein said nucleic acid molecule encodes a human polypeptide.
3. (Currently Amended) The nucleic acid of claim 1, wherein said nucleic acid molecule has the sequence of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47, or degenerate variants thereof, and wherein said nucleic acid molecule encodes the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, or SEQ ID NO: 48, respectively.
4. (Currently Amended) A substantially pure nucleic acid molecule that hybridizes in 2X SSC medium at 40°C to the polynucleotides of a sequence found within SEQ ID NO: 1, or SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47, wherein the administration of

said nucleic acid molecule to a subject leads to a decrease in the expression of methionine synthase reductase polypeptide in said subject, relative to a control subject not administered said nucleic acid molecule ~~wherein said nucleic acid comprises a region complementary to a naturally occurring mammalian methionine synthase reductase mutation or polymorphism.~~

5. (Currently Amended) The nucleic acid molecule of claim 4, wherein said nucleic acid molecule has a sequence complementary to at least ~~30~~ 50% of at least 60 contiguous nucleotides of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47 ~~or SEQ ID NO: 41.~~

35. (Cancelled)

36. (Currently Amended) A substantially pure nucleic acid molecule having a polynucleotide sequence that has at least 50% sequence identity to SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47 over the entire length of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47, respectively, wherein said nucleic acid molecule encodes a polypeptide capable of catalyzing the reductive methylation of enzymatically inactive methionine synthase-cob(II)alamin to generate enzymatically active methionine synthase-cob(III)alamin-CH₃.

37. (Currently Amended) The nucleic acid molecule of claim 36, wherein said ~~having a~~ polynucleotide sequence ~~that~~ has at least 85% sequence identity to SEQ ID NO: 1, SEQ ID NO:

41, SEQ ID NO:43, SEQ ID NO: 45, or SEQ ID NO: 47 over the entire length of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47, respectively.

38. (Currently Amended) The nucleic acid molecule of claim 37, wherein said having a polynucleotide sequence ~~that~~ has at least 95% sequence identity to SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47 over the entire length of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47, respectively.

39-40. (Cancelled)

41. (Currently Amended) A substantially pure nucleic acid molecule having a polynucleotide sequence that has at least 50% sequence identity to a sequence that is complementary to the corresponding region of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47, wherein the administration of said nucleic acid molecule to a subject leads to a decrease in the expression of methionine synthase reductase polypeptide in said subject, relative to a control subject not administered said nucleic acid molecule , wherein said nucleic acid comprises a naturally occurring mammalian methionine synthase reductase mutation or polymorphism.

42. (Currently Amended) The nucleic acid molecule of claim 41, wherein said polynucleotide sequence ~~having a polynucleotide sequence that~~ has at least 85% sequence identity to a sequence that is complementary to the corresponding region of SEQ ID NO: 1, SEQ

ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47.

43. (Currently Amended) The nucleic acid molecule of claim 42, wherein said polynucleotide sequence ~~having a polynucleotide sequence that~~ has at least 95% sequence identity to a sequence that is complementary to the corresponding region of SEQ ID NO: 1, SEQ ID NO: 41, SEQ ID NO: 43, SEQ ID NO: 45, or SEQ ID NO: 47.

44. (Cancelled)

45. (Currently Amended) The nucleic acid molecule of claim 1 or 36 ~~1, 36, or 41,~~ wherein said nucleic acid molecule encodes ~~encoding~~ a mammalian methionine synthase reductase polypeptide having at least 20 to 30% ~~20-30%~~ of the biological activity of ~~ability to~~ catalyze ~~the reductive methylation of methionine synthase cob(II)alamin to generate methionine synthase cob(III)alamin-CH₃ as the methionine synthase reductase polypeptide of SEQ ID NO:~~ 2.

46. (Currently Amended) The nucleic acid molecule of claim 45, wherein said nucleic acid molecule encodes ~~encoding~~ a mammalian methionine synthase reductase polypeptide having at least 55 to 75% ~~55-75%~~ of the biological activity of ~~ability to catalyze the reductive methylation of methionine synthase cob(II)alamin to generate methionine synthase-cob(III)alamin-CH₃ as the methionine synthase reductase polypeptide of SEQ ID NO: 2.~~

47. (Currently Amended) The nucleic acid molecule of claim 1 or 36 ~~1, 36, or 41~~, wherein said nucleic acid molecule encodes ~~encoding~~ a mammalian methionine synthase reductase polypeptide that comprises a consensus binding site for one or more cofactors selected from the group consisting of FAD, FMN, and NADPH, wherein said binding site comprises any one of SEQ ID NOs: 25-40.

48. (Withdrawn) The nucleic acid of claim 47, wherein said binding site comprises a sequence that is at least 70% identical to one of the following sequences:

- (a) FLLLYATQQGQAKAIAEEMC (SEQ ID NO: 52),
- (b) VVVVSTTGTGDPDPTARKFVKEI (SEQ ID NO: 53),
- (c) AHLRYGLLGLGDSEYTYFCNGGKIIDKRL (SEQ ID NO: 54),
- (d) LQPRPYSCASSSLFHPGKL (SEQ ID NO: 55),
- (e) FVFNIVEFLSTATT (SEQ ID NO: 56),
- (f) LRKGVCTGWLALLVASV (SEQ ID NO: 57),
- (g) IPIIMVGPGTGIAPFIGFLQHR (SEQ ID NO: 58),
- (h) SFSRDA (SEQ ID NO: 59),
- (i) APAKYVQDNIQLHGQQVARILLQENGHIYVCGDAKNMAKDV
(SEQ ID NO: 60), or
- (j) KRYLQDIWS (SEQ ID NO: 61).

49. (Withdrawn) The nucleic acid of claim 48, wherein said binding site comprises a sequence that is identical to one of the following sequences:

- (a) FLLLYATQQGQAKAIAEEMC (SEQ ID NO: 52),
- (b) VVVVSTTGTGDPDPTARKFVKEI (SEQ ID NO: 53),
- (c) AHLRYGLLGLGDSEYTYFCNGGKIIDKRL (SEQ ID NO: 54),
- (d) LQPRPYSCASSSLFHPGKL (SEQ ID NO: 55),
- (e) FVFNIVEFLSTATT (SEQ ID NO: 56),
- (f) LRKGVCTGWLALLVASV (SEQ ID NO: 57),
- (g) IPIIMVGPGTGLAPFIGFLQHR (SEQ ID NO: 58),
- (h) SFSRDA (SEQ ID NO: 59),
- (i) APAKYVQDNIQLHGQQVARILLQENGHIYVCGDAKNMAKDV
(SEQ ID NO: 60), or
- (j) KRYLQDIWS (SEQ ID NO: 61).

50-51. (Cancelled)

52. (Currently Amended) The nucleic acid molecule of claim 4 or 41 ~~51~~, wherein said ~~the administration of said nucleic leads to a decrease in the activity of said mutant~~ methionine synthase reductase polypeptide is a mutant or polymorphic methionine synthase reductase polypeptide.

53. (Currently Amended) The nucleic acid molecule of claim 4 or 41, wherein said nucleic acid molecule comprises a polynucleotide sequence the complement of which comprises a said naturally-occurring mammalian methionine synthase reductase mutation or polymorphism.

54. (New) The nucleic acid molecule of claim 36, 37, or 38, wherein said polynucleotide sequence comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism.

55. (New) The nucleic acid molecule of claim 41, 42, or 43, wherein the complement of said polynucleotide sequence comprises a naturally-occurring mammalian methionine synthase reductase mutation or polymorphism.